REMARKS

This amendment is submitted after final rejection pursuant to 37 CFR 1.116 because Applicant believes that the claims in this application are now in condition for allowance. In any event entry of this response will place the application in better form for appeal. Applicant has raised no new issues and has added no prohibited new matter. Finally the arguments that Applicant now presents are in direct response to points raised by the Examiner in the last office action and Applicant could not have filed his response at an earlier date.

The Examiner has finally rejected claims 12 and 13 as obvious under 35 USC 103 again citing HILLMAN et al in combination with BIANCHI et al and in further combination with WANG et al. Again the Examiner points to HILLMAN et al for its disclosure of both the DRPCS and HERG potassium ion channel subunits, and argues that since HILLMAN et al discloses that blockading the DRPCS potassium ion channel subunit may be effective in the treatment of tumors, one skilled in the art would also expect a blockading of the HERG potassium ion channel subunit to also be effective in the treatment of cancer. The Examiner admits that the structures of the DRPCS and HERG subunits are not the same and are in no way analogous and relies solely on his belief that DRPCS and HERG have similar functions, that is mediating rectifying delay-type

potassium current, even though the Examiner admits that the HERG subunit mediates the fast activating component of the potassium rectifying current and the DRPCS mediates the slow activating component of the potassium rectifying current. The Examiner argues that both the DRPCS subunit and the HERG subunit are both expressed in cardiac tissue, which he believes provides further evidence that the two respective subunits have similar properties, and concludes that here is a further reason why one would expect the blockading of the HERG subunit to effectively treat cancer.

The Examiner maintains that BIANCHI et al discloses that adenocarcinomas possess a rectifying current that is similar to the HERG potassium rectifying current, and further discloses blockading the potassium rectifying current of cancer cells using Compound E-4031. The Examiner then states that almost all forms of colon cancer are adenocarcinomas. WANG et al also discloses blockading the potassium rectifying current of the HERG subunit using Compound E-4031 to antagonize the HERG subunit. The Examiner concludes from this combination of all three references that it would be obvious to administer Compound E-4031 to a patient suffering from colon cancer to effectively treat the colon cancer.

The Examiner further concludes from the cited combination of references that it would be obvious to try to treat colon cancer in a patient suffering with the disease by blockading the HERG potassium ion channel subunit with Compound E-4031 since the HILLMAN et al reference discloses only two potassium ion channel

subunits: DRPCS and HERG and discloses that the blockading of the DRPCS subunit effectively treats cancers and so one skilled in the art would routinely try blockading the HERG subunit with the expectation of obtaining a similar effect against cancer.

In addition the Examiner argues that the preliminary steps in claim 13 to diagnose the colon cancer in a tissue biopsy taken from a patient suspected of suffering from colon cancer by detecting as a selective tumor marker the HERG subunit in the tissue as an indication of colon cancer, when the tissue in a healthy patient would normally not express the HERG potassium ion channel. The Examiner merely states that it is well known to test samples of bodily tissues to detect biomarkers of cancer, and so it would be obvious to perform steps (a), (b) and ©) of claim 13 to detect colon cancer in a tissue sample taken from a patient suspected of suffering from colon cancer.

Applicant strongly believes that the combination of HILLMAN et al, BIANCHI et al, and WANG et al does not lead those skilled in the art to the invention as claimed in claims 12 and 13.

One of the key points in determining whether either the treatment of colorectal cancer with E-4031 is patentable or whether the method of diagnosing the colorectal cancer is patentable is whether Applicant is the one who discovered that the HERG potassium channel is present in colorectal cancer tissue. In fact the Applicant was the one who discovered that the HERG potassium ion channel is present in colorectal cancer tissue. Prior to the

Applicant's German priority date of 31 May 2002, Applicant knows of only two prior art references that deal with the HERG subunit of potassium ion channels and carcinomas. Those two references are BIANCHI et al, cited by the Examiner, and CHERUBINI et al, 2000, Brit. J. Cancer 83(12), pp 1722 to 1729, abstract enclosed herewith. Neither of these references discloses or suggests the treatment of any kind of cancer by blockading the HERG subunit of a potassium ion channel with Compound E-4031 or any other compound, and neither of these references makes any mention of either the diagnosis of colon cancer by using the HERG subunit of a potassium ion channel as a genetic marker for colon cancer or the treatment of colon cancer by administering Compound E-4031 or any other compound to blockade the HERG subunit of a potassium ion channel. Once again at the time of the publication of both BIANCHI et al and CHERUBINI et al, it was not known in the art that colorectal tissue taken from a patient suffering from colon cancer would contain the HERG subunit of a potassium ion channel whereas the same corresponding colorectal tissue in a healthy patient, would be free of colorectal cancer, so that the presence of the HERG subunit of a potassium ion channel could function as a genetic marker for colon cancer, let alone that the blockading of the HERG subunit with Compound E-4031 would effectively treat the colon cancer.

BIANCHI et al discloses HERG ion channels in <u>tumor cell lines</u>, through not in colon cancer tumor cell lines, but most importantly not in tissue. The tumor cell lines disclosed in

BIANCHI et al originate from neuroblastoma, rhabodomyosarcoma, adenocarcinoma, lung microcytoma, pituitary tumors, insulinoma beta-cells, and monoblastic leukemia. It is mentioned that HERG is not only physiologically present in heart tissue, but in various tumor cell lines as well. See page 820, Figures 1 and 6. The conclusion that if in one adenocarcinoma, such as breast adenocarcinoma, HERG channels can be found; that HERG potassium ion channels will automatically be found in other types of adenocarcinoma, such as colorectal adenocarcinoma, is purely hypothetical on the Examiner's part, and scientifically unfounded in view of the completely different types of tissue: breast tissue versus colorectal tissue.

Applicant points out that cell lines growing in a dish are usually homogeneous, and in this respect are very different from primary cells which are quite diverse. A solid tissue with an organism (tumor) is not the same as cells in a dish. One would likely expect that the concentration of a drug used to block tumor progression might be significantly higher than that needed to block proliferation of a tumor cell line, simply because the drug cannot penetrate physically as well into the solid tumor. Thus there is a further basis to distinguish BIANCHI et al from the presently claimed invention.

CHERUBINI et al discloses HERG potassium ion channels in endometrial cancers. The reference data show that HERG potassium channels may be found in some human tumors (in tissue, not in tumor

cell lines) as well. Colorectal carcinoma were not investigated or even mentioned. Thus neither BIANCHI et al or CHERUBINI et al discloses that HERG potassium ion channel subunits are present in tumors invading colorectal tissue.

Furthermore neither BIANCHI et al nor CHERUBINI et al suggests that the HERG potassium ion channel would be present in colorectal tissue and that the corresponding healthy tissue would not include the HERG potassium ion channel. Once again neither reference either discloses or even makes mention of the presence of the HERG potassium ion channels in colorectal cancer tissue. Applicant emphasizes that adenocarcinoma tissue normally does not contain the HERG potassium ion subunits. Thus BIANCHI et al does not disclose that tumor cells routinely contain HERG potassium ion channels.

Therefore the Applicant's discovery of HERG potassium ion channels in colorectal tissue was surprising and unobvious, and not merely expected in view of the disclosure in the prior art (e.g. BIANCHI et al) that adenocarcinoma tissue taken from the breast contained the HERG potassium ion channel. None of the cancers specifically disclosed in Figs 1 and 6 of BIANCHI et al are colorectal cancers. The Examiner argues on page 3 of the office action that it is known in the art that adenocarcinomas form 90 to 95% of colorectal cancers. However, the disclosure in BIANCHI et al of adenocarcinomas with HERG potassium ion channel subunits includes only six cell lines and creates a misimpression that HERG

ion channels are expressed in all cancer cell lines and that HERG expression is essential for all oncogenic transformation. This limited disclosure of HERG potassium ion channels in tumorous cells in BIANCHI et al leads to speculation that HERG potassium ion channels would routinely be expected to be found in any adenocarcinoma, including adenocarcinomas of the colon or rectum. Applicant provides more detail on this point in his Declaration Under 37 CFR 1.132 which accompanies this amendment.

Neither the WANG et al nor the BIANCHI et al reference discloses the use of E-4031 to treat colorectal cancer in particular or any other cancer. These references merely show that E-4031 antagonizes the HERG potassium ion channel. In fact only BIANCHI et al even suggests any connection between the HERG potassium ion channel and cancer, including adenocarcinoma of the breast, though the reference clearly lacks any specific mention of colorectal cancers.

Applicant maintains that his arguments against the HILLMAN et al reference are sound for three reasons:

(1) the HERG potassium ion channel functions differently from the DRPCS potassium ion channel, fast-acting versus slow acting, implying a different mechanism of action, and a lack of equivalence;

(2) the structure of the compound E-4031, a small aromatic molecule with a methanesulfoanilide functional group, which antagonizes the HERG potassium ion channels, is vastly different from the antibody fragments (proteins) disclosed in HILLMAN et al in col. 20, lines 17 to 28 to antagonize DRPCS potassium ion channels; and

(3) the structure of the HERG potassium ion channel itself, shown in Fig. 3 of BIANCHI et al, is very different from the structure of the DRPCS potassium ion channel disclosed in Figs. 1A and 1B of HILLMAN et al.

According to figure 1 of that Hillman patent, the tiny little DRPCS clone bears no sequence similarity to the HERG subunit at all. The HERG subunit is a pore-forming (alpha) subunit, meaning that it contains a pore that conducts current. On the other hand, DRPCS functions as a beta subunit, meaning that it can affect the properties of certain alpha subunits but contains no pore of its own. The HERG subunit is definitely an alpha subunit, not a beta subunit. Even though the HERG subunit bears some similarity to the voltage-gated K+ channel family (whose members typically conduct K+ ions out of the cell), the HERG subunit actually conducts inward K+ current.

It is also not clear from HILLMAN et al that DRPCS can coassemble with HERG at all; rather, it appears that DRPCS

associates with a different alpha subunit called KCNQ. Thus the HILLMAN et al patent has little or nothing to do with the Applicant's presently claimed invention in terms of the structure of the ion channel subunit, the function of the ion channel subunit or the compound used to block the ion channel subunit. Thus the combination of HILLMAN et al with BIANCHI et al and WANG et al would still not lead to the presently claimed invention where Compound E-4031 is used to blockade the HERG potassium ion channel subunit to treat patients with colon cancer.

The BIANCHI et al reference shows only that HERG is overexpressed in tumors and that E-4031 can efficiently block HERG, and so the Examiner make the connection that E-4031 can block HERG potassium ion channels expressed in colorectal tumor cells. However, it is not disclosed in either BIANCHI et al or WANG et al that this blockading treatment of the HERG potassium ion channel with Compound E-4031 would have any effect on diminishing the growth of any cancer, let alone cancer in colorectal tissue. Just because HERG is overexpressed in some cancer cell lines does not necessarily mean that HERG potassium ion channels would make a good target for an anticancer drug to treat cancer, in particular colorectal cancer, especially when it was not even known at the time of the present invention that tumors of the colon and rectum contained the HERG potassium ion channel subunit.

The Examiner has cited two recent decisions by the US Courts, including KSR International Co. V. Teleflex Inc., 82 USPQ

2d 1385 (US Supreme Court 2007) and Daiichi Sankyo Co. V. Apotex Inc., 84 USPQ 2d 1285 (CAFC 2007) that he believes support his position that he has a right to combine the three prior art references to establish that the invention as presently claimed is obvious. The Examiner argues that the KSR decision holds that where the prior art discloses a limited number of predictable choices, that it would be obvious to try the choices to see if a beneficial result will be obtained. The Examiner argues from the prior art cited that two potassium ion channels, HERG and DRPCS are disclosed, and that from the three cited prior art references it would be predictable that administering compound E-4031 to a patient with colorectal cancer would be effective to treat the disease. Of course it was not even known at the time of the Applicant's invention that colorectal cancer tissue even contained the HERG potassium ion channel, and as explained hereinabove it would not have been predictable that the colorectal cancer tissue contained the HERG potassium ion channel, so Applicant has a strong argument to distinguish this case from the facts in the KSR decision. Furthermore the result of successful treatment of colorectal cancer would not be predictable from the combination of HILLMAN et al, BIANCHI et al and WANG et al because the HERG potassium ion channel and the DRPCS potassium ion channel disclosed in HILLMAN et al are so different in terms of structure and function, as well as the fact that the antagonists of the DRPCS potassium ion channel disclosed in HILLMAN et al are structurally

very different from E-4031 and so the antagonists are not art-recognized equivalents. As a result the Applicant's invention would not be predictable from the prior art combination of references.

Much the same story relates to the Daiichi decision. In that decision the court held that two quinoline antibiotics, ofloxacin and ciprofloxacin, are art-recognized equivalents, and the fact that ofloxacin was useful to locally treat bacterial ear infections in patients, without causing side effects, was obvious because ciprofloxacin was already known to posses the same pharmaceutical utility, locally treating the same bacterial ear infections. Thus both medications have a quinoline nucleus and both medications treat the same bacterial infections by inhibiting the bacterial enzyme gyrase. The Court concluded that in view of the prior art disclosure of ciprofloxacin, it would have been obvious to treat the ear infections using ofloxacin according to the claimed method of treatment.

Applicant believes that the present case is entirely different because the structures of the E-4031 and the structures of the antibody fragments disclosed in HILLMAN et al are entirely different. Furthermore the HERG potassium ion channel that Applicant blockades with E-4031 is not structurally the same or functionally equivalent to the DRPCS potassium ion channel blockaded by antibody fragments according to HILLMAN et al thus neither of the cited decisions supports the Examiner's reasoning

that one "skilled in the art" would combine the HILLMAN et al, BIANCHI et al and WANG et al references, and neither of the cited decisions supports the Examiner's conclusion that the presently claimed invention would be obvious in view of the combination of the three references.

Report of Telephone Interview

Applicant wishes to thank Examiners Sutton and Krass for conducting a telephone interview with the Applicant's undersigned attorney on 9 July 1008. During the interview the Examiners and the undersigned discussed the patentability of both claims 12 and 13 over the cited prior art. The undersigned emphasized that no one before the present Applicant ever determined that the HERG potassium ion channel was present in cancerous colorectal tissue and that just because the prior art, such as BIANCHI et al and WANG et al disclose that Compound E-4031 may blockade the HERG potassium ion channel in some cancers, does not mean any of the following:

(1) that either of these references discloses the blockade of the HERG potassium ion channel to treat any kind of cancer, let alone treat colorectal cancer;

(2) that either of these references discloses the blockade of the HERG potassium ion channel in cancerous colorectal tissue;

(3) that all cancers in general and that all carcinoma in particular contain the HERG potassium ion channel.

The undersigned then turned to discussion to the HILLMAN et al reference and emphasized that the HERG subunit is an α-subunit (pore-forming) and that the DRPCS subunit is a β-subunit (no pore forming) and that the two subunits are not functional equivalents. The undersigned stressed that the structure of the DRPCS subunit is very different from the structure of the HERG and that the structure of the blockading E-4031, which Applicant uses to blockade HERG is completely different from the structure of the polypeptides used to block the DRPCS. In view of the above the undersigned argued that Applicant's presently claimed invention is patentably distinguishable over the cited prior art.

Next the undersigned referred to the Applicant's Declaration Under 37 CFR 1.132 and his curriculum vitae as an oncologist and cancer surgeon, and the Applicant's reasons for concluding that the combination of the cited prior art references provides no basis to support the obviousness rejection. Applicants noted that in the field of cancer treatment there is a good deal of unpredictability and uncertainty with respect to ion channels and noted the Applicant's data in the application showing that Applicant has found that the HERG potassium ion channel is a very

good genetic marker for detecting colon cancer and a very good starting point for the treatment of colorectal cancer.

The Examiners considered Applicant's arguments over the telephone as well as Applicants' written arguments in a draft version of the present amendment. The only significant suggestion that the two Examiners had to facilitate prosecution of this application required Applicant's amending claim 12, second and last line to add following "colorectal cancer" - having at least one HERG potassium channel -. The undersigned indicated to the Examiners that such a change appeared to be acceptable, but indicated that he will check with the Applicant to see if he will agree to this change in claim 12, last line.

The next subject matter that the Examiners and the undersigned discussed included the subject matter of dependent claim 13, directed to a method of treating colorectal cancer where the first step is the diagnosis of the colorectal cancer by using the HERG potassium ion channel as a selective tumor marker. The undersigned indicated to the Examiners that Applicant was concerned about independently protecting this concept of the invention as well and not merely administering the Compound E-4031 to treat the tumor. The Examiners suggested that the Applicant make the analogous change to claim 13 as the change proposed for claim 12.

The Examiners also indicated that they will consider Applicant's rejoining claims directed to a method of diagnosing a colorectal carcinoma having at least one HERG potassium channel in a patient suspected of suffering from colorectal cancer. This subject matter was originally covered in claims 1 through 3 and then covered in claims 8 through 11. The Examiners indicated that if Applicant limits all of the diagnostic claims to a method of diagnosing a colorectal carcinoma having at least one HERG potassium channel in a patient suspected of suffering from colorectal cancer, they will consider Applicant's rejoining these withdrawn claims with claims 12 and 13 directed to a method of treating colorectal cancer having at least one HERG potassium channel in a patient in need of said treatment. Applicants are submitting new claims 14 through 17 which are directed to a method of diagnosing a colorectal carcinoma having at least one HERG potassium channel in a patient suspected of suffering from colorectal cancer. Antecedent basis for claims 14 through 17 may be found in the specification on page 2, line 24 through page 4, line 7 Now Applicant ask that the Examiners accept that claims 14 through 17 be included together with claims 12 and 13 and that all claims be held allowable over the prior art.claims12 through 17 are all patentably distinguishable over the cited prior art and should be allowed.

Applicant believes that all claims now presented are in condition for allowance and a response to that effect is earnestly solicited.

Applicant encloses a petition to obtain a two month extension of the term for response (small entity) to the outstanding official action as well as PTO Form 2038 to charge the cost of obtaining the extension to the credit card of the undersigned attorneys.

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Enclosures:
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PTO-1449 and 1 reference
Declaration Under 37 CFR 1.132

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